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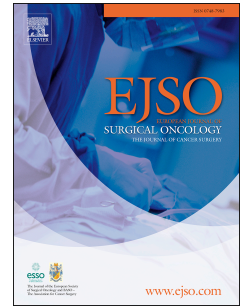
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Perioperative Therapies – Enhancing the Impact of Cancer Surgery with Repurposed Drugs

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Abstract

Surgical resection remains the major modality for modern curative treatment for solid tumours. However, post-surgical recurrence, even following clear-margin resection and adjuvant treatment, remains common in many types of cancer. Reducing recurrence rates, therefore, offers the potential to increase cure rates and increase overall survival. Perioperative therapies, simple interventions during the perioperative period, are designed to address some of the factors which influence post-surgical recurrence. A range of perioperative therapies are introduced and the rationale for further clinical investigation outlined.

Keywords: Perioperative period, surgical resection, metastases, cancer recurrence, drug repurposing

Introduction

Even with the promise of precision medicine and onco-immunotherapy, surgical resection remains the major modality for modern curative treatment for solid tumours. For many types of cancer clear-margin (R0) resection represents the best chance for patients to achieve long-term survival. It remains true that despite recent significant advances, for example in immuno-oncology, metastatic cancers are difficult to treat and long-term survival poor. In all too many cases, even curative resection with clear margins is a prelude to disease recurrence, even when surgery is followed by adjuvant treatment.

The phenomenon of post-surgical distant recurrence is common in a number of cancers, including breast, non-small cell lung cancer, osteosarcoma and others (Table 1). In osteosarcoma, for example, a disease in which there have been no significant improvements in overall survival for more than 30 years, local recurrence post-surgery occurs in 6% of cases, compared to a distant recurrence rate of 47%¹. Across a broad range of solid tumours the pattern of early distant recurrence following surgical resection is remarkably consistent and yet there has been little sustained effort to address the issue. Definitive R0 surgical resections and *the reduction of recurrence rates*, therefore, hold the potential *to significantly improve overall survival by increasing cure rates*. A range of interventions in the perioperative period, which we term perioperative therapies, may be a means to this end.

In contrast, there has been a concerted effort to develop systemic therapies to address the unmet needs associated with metastatic disease. Molecularly targeted drugs, onco-immunotherapies, proton beam radiation and other high-cost interventions have been a particular focus for development, driven by commercial as well as patient agendas. Results to date have been mixed, and the impact on overall population survival has, on the whole, been very modest.

There is also increasing concern about the long-term economic burdens associated with these high-cost interventions. Such concerns, driven both by the rising prices and costs of new drugs and technologies and by the projected increases in cancer incidence, are common to both high income and to low and middle income countries alike. In the absence of significant price reduction strategies these new treatments are likely to impose even more significant strains on stressed health systems in high income countries, and to rule out such treatments in low and middle income countries for many years to come. In this context it becomes imperative to explore other strategies to achieve substantial clinical benefit but with a cost profile that imposes a lower level of financial stress on health systems.

Perioperative intervention to reduce the risk of post-surgical recurrence is one such strategy. In contrast to neoadjuvant therapies, which are primarily intended to downstage tumours to facilitate successful resection, perioperative therapies are designed to decrease the risk of disease recurrence after successful resection. We should note that even when patients achieve pathological complete response (pCR) following neoadjuvant therapy there remains a risk of relapse, for example in breast cancer there is a 15% risk of relapse (local or distant) after achieving pCR. The need, therefore, for perioperative therapies exists even in those cancers in which neoadjuvant therapies are established as the standard of care.

Factors Influencing Post-surgical Recurrence

There are multiple mechanisms associated with post-surgical recurrence, as shown in Figure 1, primarily associated with the inflammatory wound-healing response that follows surgical incision.

This wound-healing response initiates a cascade of pro-angiogenic signalling, the upregulation of catecholamines and pro-metastatic prostaglandins and the onset of cell-mediated immunosuppression.

Other factors include psychological distress, the impact of analgesics and anaesthesia, surgical hypothermia, hypoxia, surgically-induced increased lysyl oxidase (LOX) activity, tissue damage and the release of cancer cells into the circulation. A number of reviews have outlined these and other relevant mechanisms in some detail, drawing particularly on data from animal models of post-surgical relapse². We should note that while poor surgical technique and lack of expertise also have an impact on outcomes, the mechanisms described in Figure 1 occur even after skilfully executed clear-margin tumour resection. We may speculate that the gains from improvements in surgical expertise and from the adoption of perioperative therapies are likely to be additive.

Perioperative Therapies

This knowledge of the mechanisms opens the door to a range of interventions which target relevant pathways such that one or more of these pro-metastatic pathways is inhibited, thereby reducing the risk of loco-regional recurrence or metastatic spread. Significantly, a number of such interventions are supported by evidence of efficacy in clinical trials (Table 2). For instance, a Phase III trial of preoperative depot progesterone, in women under-going mastectomy, showed disease-free survival and overall survival were improved in node-positive women³.

There are also mechanistic reasons to support the use of other agents in the perioperative period, for example the use of tranexamic acid to reduce intra-operative blood loss in liver cancer surgery which is known to increase the risk of recurrence (which may due to increased tumour shedding or the impact of peripheral blood transfusion). Additionally there are a number of non-pharmacological perioperative interventions which may also be efficacious in reducing distant recurrence, including regional anaesthesia and enhanced recovery programs initiated before surgery, which includes nutritional support, physical training and stress management.

These various interventions have a number of features in common, in addition to the existing pre-clinical and clinical evidence in their favour. The first is that these are generally interventions of short duration, in the case of ketorolac and depot progesterone a single administration prior to surgical incision, in the other cases the interventions are of one or two weeks duration prior to and/or following surgery. Secondly, the agents used are low in cost – in fact the examples cited are all generic and generally available for repurposing globally⁴. Together the low cost of the drugs and the short duration of treatment renders this approach affordable in all parts of the world. Indeed from a global perspective most patients present with locally advanced and inoperable, metastatic disease. The use of this intervention strategy more widely in surgical models of care has the potential to provide highly cost effective improvements in control and cure.

Clinical trials of perioperative therapies require little investment in terms of drug costs or changes to clinical procedure or the use of new surgical techniques. However, clinical trials are costly to establish and administer and the use of low-cost repurposed drugs means there is little financial incentive for investment from the pharmaceutical industry. Furthermore such clinical trials require long-term follow-up of patients to assess recurrence rates and overall survival, often a challenge in

many countries where patients are lost to follow up. Nevertheless, where this can be overcome, the use of modern clinical trial designs, notably multi-arm, multi-stage trials, is particularly suitable for these types of interventions and can maximise the informational value and minimise the administrative burdens associated with clinical research. International collaborations can help focus on those cancers with the greatest potential for benefit and assess multiple possible interventions in parallel.

Other challenges to implementation include the interdisciplinary nature of perioperative treatments – of necessity such trials require the close cooperation of surgeons, anaesthesiologists and medical oncologists. In which medical specialism do these treatments sit? It is also the case that in many institutions, particularly in non-academic centres, there is a paucity of surgical trial experience compared to medical oncology experience.

Discussion

Owing to the complexity of the surgical stress response, it will also be important to conduct biological studies to have a better understanding of the physiological processes driving local recurrence and metastatic spread. While immune suppression at the time of surgery is one major aspect to explore, other important mechanisms are also involved. Lymphatic vessel dilation or interaction between platelets and tumour cells are examples of additional mechanisms likely to be major contributors to this phenomenon. In parallel to clinical trials, gathering additional biological data will be of the outmost importance to learn from possible failures and to build on possible successes. The development of surrogate markers of clinical benefit, particularly blood-borne biomarkers (circulating tumour cells etc), may further improve the response rates and aid in selecting those patients most likely to see improved outcomes from such interventions.

In an age of precision medicine, immunotherapy and high-technology, perioperative therapies with off-patent generic drugs are decidedly low-tech and easy to deliver. In some cases, for example the pre-incisional use of ketorolac, clinical adoption following evidence of efficacy will not require additional licensing or market authorisation procedures and therefore adoption may proceed quickly and cheaply via inclusion in guidelines and updates to current practice. However, the low-cost/low-tech model and the long duration of follow-up for studies act as disincentives to investment from the commercial sector, particularly the pharmaceutical industry. Given the potential benefits to patients, and the potential cost-effectiveness associated with these treatments, it is a matter of some urgency that clinical research in this area is expanded. It is clear that this research will have to rely mainly on public and philanthropic funds. It will also require the intellectual engagement of surgeons, medical oncologists and anaesthesiologists alike. This is particularly germane to low and middle income countries struggling with increasing cancer burdens and urgently in need of new affordable and efficacious treatment options that compress pathways and improve the impact on outcomes of current models of care.

Recurrent and metastatic disease has immense costs to society, not just in the increased morbidity and mortality to affected patients, but also in the economic costs associated with additional treatments, lost income, family disruptions and other negative social impacts. The promise of short-term perioperative therapy is that it enhances the chances that curative-intent surgery leads to definitive cure at a cost that is affordable in all economies.

Conflict of interest statement

The authors have no financial interest to declare in relation to the content of this article.

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Table 1 Patterns of recurrence after R0 resection and standard treatment in selected cancer types

Cancer	Follow-up	Locoregional only	Distant only	Ref
Osteosarcoma	10 year	6%	47%	1
Rectal	5 year	11%	32%	5
Oesophageal	5 year	21%	43%	6
NSCLC	5 year	7%	13%	7
Breast	10 year	8%	18%	8

Table 2 Examples of pharmacological perioperative interventions with evidence supporting their role in preventing distant recurrence

Interventions	Cancer Type	Type of evidence	Results	Ref
Ketorolac	Breast	Human, retrospective	Reduced recurrence rate (adjusted HR, 0.37; 95% CI, 0 to 0.79, P = 0.019)	9
Depot progesterone	Breast	Human, trial	Improved DFS for node-positive patients (adjusted HR, 0.71; 95% CI, 0.53 to 0.95; P = 0.02)	3
Atrial Natriuretic Peptide	NSCLC	Human, retrospective	2-year RFS significantly greater in ANP-treated patients than in control patients (91% vs. 75%, P = 0.018)	10
Cimetidine	Colorectal	Human, trial	Meta-analysis of five trials shows significant improved OS (HR, 0.53; 95% CI 0.32 to 0.87).	11
Aspirin	Rectal	Human, retrospective	Improved 5-year PFS (86.6% vs 67.1%; HR=0.20; 95% CI=0.07–0.60), OS (90.6% vs 73.2%; HR=0.21; 95% CI=0.05–0.89) and a lower metastatic risk (HR=0.30; 95% CI=0.10–0.86).	12
Arginine	Head & neck	Human, trial	Improved OS (HR: 2.6; 95% CI: 1.1, 6.1), DFS (HR: 4.2; 95% CI: 1.4, 12.5)	13
Calcitriol	Head & neck	Human, trial	Increased time to recurrence (treatment group median 620 days, control 181 days, P=0.048)	14
Propranolol +/- etodolac	Several	In vivo, human trials ongoing	Significantly increased murine survival rates (P = 0.0315)	15
IL2	Renal cell	Human, trial	Improved five year tumour-specific survival rate (86% vs 73%, P=0.043) and PFS rate (81% vs 62%, P=0.019).	16

Figure 1:

Post-surgical recurrence following R0 resection, potential mechanisms of action

